RSC Advances

PAPER

View Article Online
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Cite this: *RSC Adv.*, 2018, **8**, 21754

Expanding the synthesizable multisubstituted benzo[*b*]thiophenes *via* 6,7-thienobenzynes generated from *o*-silylaryl triflate-type precursors†

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Received 11th May 2018
Accepted 6th June 2018

DOI: 10.1039/c8ra04035d

rsc.li/rsc-advances

Various 2,3-disubstituted 6,7-thienobenzynes have been efficiently generated from the corresponding *o*-silylaryl triflate-type precursors by activation with fluoride ions. The method has expanded the scope of synthesizable multisubstituted benzothiophenes, including those with various heteroatom substituents, and can be applied to the synthesis of EP4 antagonist analogs.

Introduction

Benzo[*b*]thiophene is one of the structural units frequently found in molecules applied in various research fields, including medicinal chemistry and materials science.[1–3] Although multisubstituted benzothiophenes are promising compounds as pharmaceutical and organic material candidates, their synthetic approaches are limited.[4] To improve this situation, we previously reported a facile method to prepare various tetrasubstituted benzothiophenes *via* thienobenzyne intermediates such as **I** (Fig. 1A).[5] Thienobenzynes **I** were efficiently generated from *o*-iodoaryl triflate-type precursors by treatment with a silylmethyl Grignard reagent at −78 °C, rendering a diverse range of tetrasubstituted benzothiophenes easily available.[6] We considered that the use of *o*-silylaryl triflate-type thienobenzyne precursors would further expand the scope of the synthesizable benzothiophenes (Fig. 1B). This is because generation of arynes from this type of precursor has been generally achieved under mild conditions using a basic activator such as the fluoride ion.[7–9] Indeed, a wide range of aromatic compounds have become easily available *via* the transformation of arynes generated from *o*-silylaryl triflate-type precursors. Herein, we report the synthesis of *o*-silylaryl triflate-type 6,7-thienobenzyne precursors, the generation of aryne species from these precursors, and the application of the method to the synthesis of various benzothiophenes including potent analogs of a prostaglandin E receptor subtype 4 (EP4) antagonist.

Results and discussion

Synthesis of thienobenzyne precursors

Similar to our previous synthesis of *o*-iodoaryl triflate-type 6,7-thienobenzyne precursors, *o*-silylaryl triflate-type precursors **2a–d** were successfully prepared from the corresponding 2,3-disubstituted 6-hydroxybenzo[*b*]thiophenes **1a–d** (Schemes 1 and 2).[5] Benzothiophenes **2a–c** were prepared from 6-hydroxybenzothiophenes **1a–c** according to the facile synthetic method for *o*-silylaryl triflates from phenols as reported by Garg and coworkers; carbamate formation using isopropyl isocyanate, regioselective *C*-silylation *via ortho*-lithiation, removal of the directing group, and triflylation (Scheme 1).[10] Although preparation of benzothiophene **2d**, bearing a chloro and an amide group, from phenol **1d** by the same method was unsuccessful at the step of *C*-silylation *via ortho*-lithiation, the *C*-

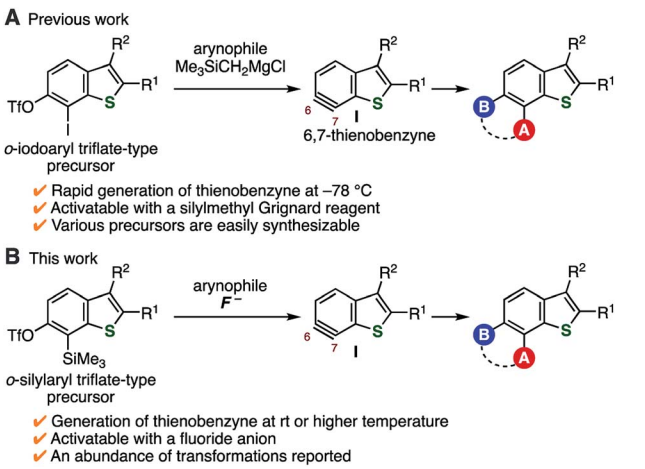

Fig. 1 Transformations *via* thienobenzyne intermediates **I**. (A) Our previous work using *o*-iodoaryl triflate-type precursors. (B) This work using *o*-silylaryl triflate-type precursors.

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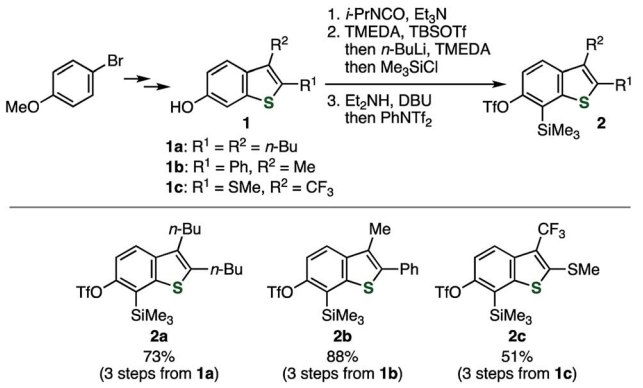
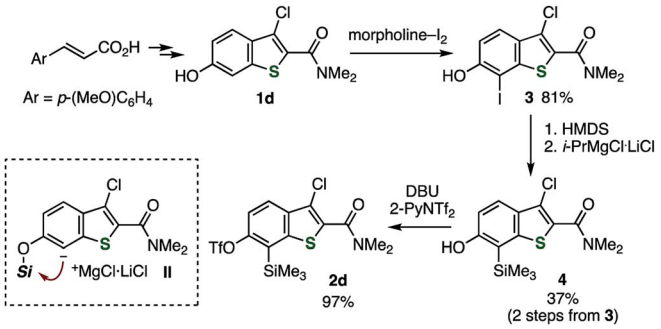
† Electronic supplementary information (ESI) available: Experimental procedures, characterization for new compounds including NMR spectra. See DOI: 10.1039/c8ra04035d



Scheme 1 Synthesis of thienobenzyne precursors **2a–c**. See the ESI† for details.



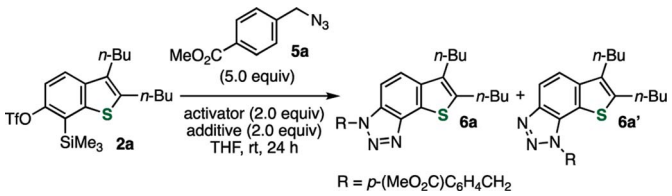
Scheme 2 Synthesis of thienobenzyne precursor **2d**. See the ESI† for details.

silylated product was obtained by an alternative method (Scheme 2).[11] Thus, regioselective iodination of phenol **1d** with a morpholine–iodine complex, followed by *O*-silylation and treatment with the turbo Grignard reagent to promote the iodine–magnesium exchange reaction and subsequent retro-Brook rearrangement *via* the anionic intermediate **II**, afforded *o*-silylphenol **4**, leaving the chloro and amide groups untouched. Finally, triflylation of **4** afforded the desired **2d**.[12,13] Performing the retro-Brook rearrangement and subsequent *O*-triflylation in one-pot procedure[12a] afforded **2d** in 13% yield.

Optimization of the reaction conditions for generation of thienobenzynes

The efficient conditions for generating 6,7-thienobenzyne were screened for the reaction between precursor **2a** and azide **5a** in tetrahydrofuran (THF) at room temperature, which revealed that various fluoride sources or cesium carbonate with 18-crown-6 were effective as an activator (Table 1). For example, the activation of **2a** with potassium fluoride in the presence of 18-crown-6 afforded the desired cycloadduct **6a** with a small amount of regioisomer **6a′** (entry 1). The regioselectivity was slightly lower than that observed in the reaction using *o*-iodoaryl triflate-type 6,7-thienobenzyne precursor probably because the reaction triggered by silicate formation was conducted at a higher temperature. Tetra(*n*-butyl)ammonium

Table 1 Optimization of the reaction conditions



Entry	Activator	Additive	Yield[a] (%)
1	KF	18-Crown-6	78 (89 : 11)
2	n-$Bu_4N[Ph_3SiF_2]$	—	73 (90 : 10)[b]
3[c]	n-Bu_4NF	—	69 (91 : 9)
4	KF	—	0
5	CsF	—	84 (90 : 10)[b]
6[d]	CsF	—	74 (89 : 11)
7	Cs_2CO_3	18-Crown-6	75 (89 : 11)

[a] Yields were determined by ^{1}H NMR analysis, unless otherwise noted. [b] Isolated yield. [c] Reaction was performed at 0 °C. [d] Azide **5a** (2.0 equiv.) was used.

difluoro(triphenyl)silicate and tetra(*n*-butyl)ammonium fluoride also served as good activators without any additives (entries 2 and 3). While using potassium fluoride alone was ineffective (entry 4), **2a** was efficiently activated with cesium fluoride, resulting in the highest combined yield of cycloadducts **6a** and **6a′** (entry 5). Considering that the generation of benzyne from *o*-(trimethylsilyl)phenyl triflate with cesium fluoride in THF was reported as inefficient,[9a] this result suggests that thienobenzyne precursor **2a** is more easily activatable than the simple *o*-silylphenyl triflate. Decreasing the amount of azide **5a** to 2.0 equiv. slightly lowered the yield of **6a**/**6a′** (entry 6). In addition, 6,7-thienobenzyne was also generated efficiently under fluoride-free conditions using cesium carbonate and 18-crown-6 (entry 7).[9a]

Synthesis of various multisubstituted benzothiophenes *via* thienobenzynes

Under the optimal conditions, various arynophiles reacted efficiently with thienobenzyne generated from **2a** to afford multisubstituted benzothiophenes in high yields (Fig. 2). These include cycloadducts **7**, **8**, **9**/**9′**, and **10** obtained from the reactions with 2,5-dimethylfuran, *N*-phenylpyrrole, *N*-(*tert*-butyl)-α-phenylnitrone, and 1,1-dimethoxyethylene, respectively. The nucleophilic addition of morpholine to the 6,7-thienobenzyne also took place, affording 6-morpholinobenzothiophene **11** as the major product. The regioselectivity observed using unsymmetrical arynophiles and the nucleophile showed similar trends to their reactions with the same thienobenzyne species generated from the *o*-iodoaryl triflate-type precursor.[5]

An abundance of utilizable transformations is a great advantage of using *o*-silylaryl triflates as aryne precursors over the other types. Indeed, the utility of *o*-silylaryl triflate-type 6,7-thienobenzyne precursor was demonstrated through several unique transformations that we recently developed (Fig. 3).[14] For example, the Michaelis–Arbuzov-type reaction of the

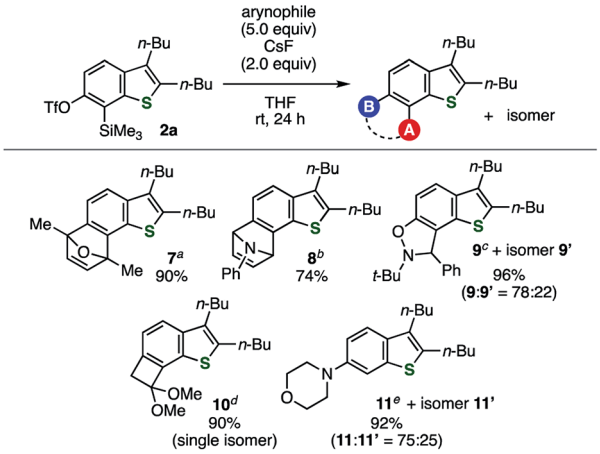


Fig. 2 Reactions of thienobenzyne generated from **2a** with various arynophiles. (a) Reaction with 2,5-dimethylfuran. (b) Reaction with *N*-phenylpyrrole. (c) Reaction with *N*-(*tert*-butyl)-α-phenylnitrone. (d) Reaction with 1,1-dimethoxyethylene. (e) Reaction with morpholine.

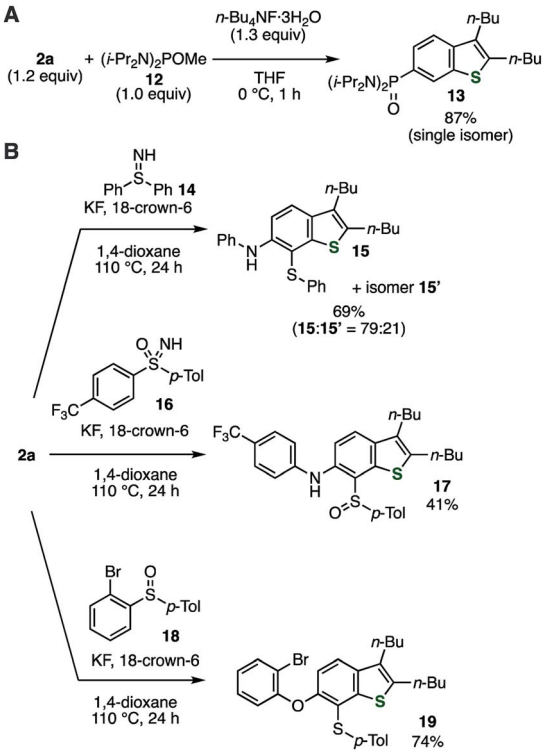


Fig. 3 Transformations *via* thienobenzyne generated from **2a**, involving C–P, C–S, C–N, and C–O bond formations. (A) Reaction with alkoxyphosphine **12**. (B) Reactions with sulfilimine **14**, sulfoximine **16**, and sulfoxide **18**. See the ESI† for details.

thienobenzyne generated from **2a** with alkoxyphosphine **12** proceeded smoothly, affording a high yield of arylphosphonic diamide **13** as the sole product (Fig. 3A).[14a] Furthermore, difunctionalizations of the thienobenzyne intermediate with sulfilimine **14**,[14b] sulfoximine **16**,[14c] and sulfoxide **18**[14d] resulted in the selective formation of thioaminated or oxythiolated benzothiophenes **15**/**15′**, **17**, and **19**, respectively, which are

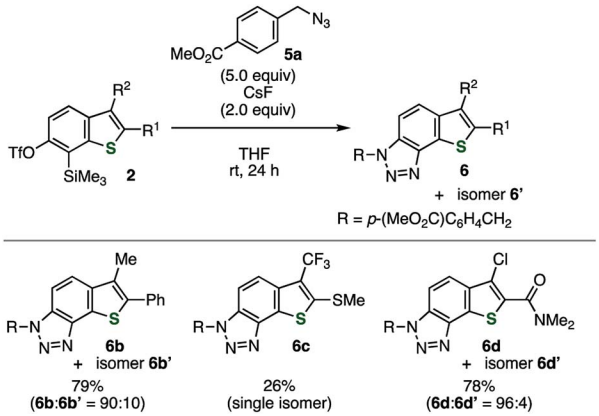


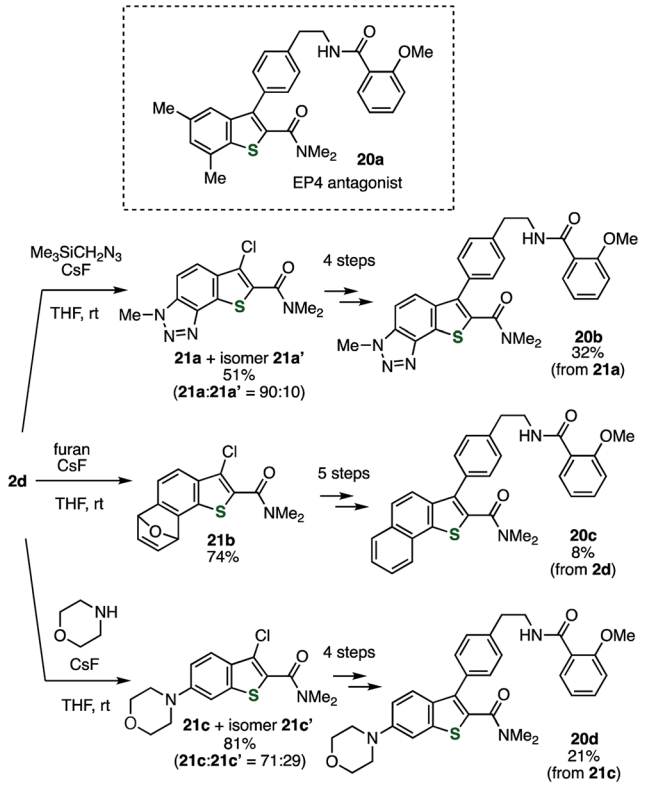
Fig. 4 Cycloadditions of various thienobenzynes generated from precursors **2b–d** with azide **5a**.

difficult to prepare by conventional methods (Fig. 3B). The yields of thioaminated products **15**/**15′** and **17** were improved under modified conditions wherein the reactions were carried out at a higher temperature in 1,4-dioxane.

Various 2,3-disubstituted 6,7-thienobenzynes were also generated from precursors **2b–d** (Fig. 4). The reactions of these thienobenzynes with azide **5a** afforded triazole-fused 3-methyl-2-phenyl-, 2-methylsulfanyl-3-trifluoromethyl-, and 3-chloro-2-(dimethylamino)carbonylbenzothiophene derivatives **6b**/**6b′**, **6c**, and **6d**/**6d′**, respectively, in a regioselective manner. Cycloadduct **6c** was obtained as a single isomer along with complex mixtures of side-products probably due to the effect of the electron-withdrawing trifluoromethyl group. A similar trend was observed in our previous study,[5] wherein **6c** was obtained without formation of the regioisomer using *o*-iodoaryl triflate-type aryne precursor activated with a silylmethyl Grignard reagent.

Synthesis of the analogs of an EP4 antagonist

The utility of this method was demonstrated in the facile diversification of the benzo-moiety of the EP4 antagonist **20a** developed by Li and coworkers (Scheme 3).[15] The analogs **20b–d** with methyltriazole-fused, benzo-fused, or morpholino-substituted benzothiophene structure, respectively, were easily prepared *via* the reactions of the thienobenzyne intermediate generated from **2d** with (trimethylsilyl)methyl azide, furan, and morpholine, affording adducts **21a–c** as the major products. According to the modified method reported previously for the derivatization of **21a** to **20b**,[5] EP4 antagonist analogs **20c** and **20d** were prepared by the Suzuki–Miyaura cross-coupling, the Mitsunobu-type C–N bond formation followed by treatment with hydrazine, and amidation. Evaluations of the EP4 receptor binding affinities showed that benzo-fused analog **20c** ($K_i = 0.18$ μM) is a potent EP4 antagonist comparable to the original compound **20a** ($K_i = 0.25$ μM), while methyltriazole-fused analog **20b** ($K_i = 0.47$ μM) and morpholino-substituted analog **20d** ($K_i = 0.70$ μM) are slightly weaker antagonists than **20a**.[16] This result suggests a possibility for developing more potent EP4 antagonists by further modification of the benzo-moiety of **20a**.



Scheme 3 Synthesis of the analogs of EP4 antagonist **20a**. See the ESI† for details.

Conclusions

This study showed that 7-silyl-6-triflyloxybenzo[*b*]thiophenes served as useful precursors of 6,7-thienobenzynes, thus expanding the range of synthesizable multisubstituted benzothiophenes. The utility of the method was demonstrated for the synthesis of various heteroatom-substituted benzothiophenes and the facile structural diversification of an EP4 antagonist that resulted in identification of a potent analog.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by AMED under Grant Numbers JP18am0101098 (Platform Project for Supporting Drug Discovery and Life Science Research (BINDS)) and JP18gm0910007 (CREST; T. Kobayashi and T. H); JSPS KAKENHI Grant Numbers 15H03118 and 18H02104 (B; T. H.), 16H01133 and 18H04386 (Middle Molecular Strategy; T. H.), and 26350971 (C; S. Y.); Suntory Foundation for Life Sciences (S. Y.); Naito Foundation (S. Y.); and the Cooperative Research Project of Research Center for Biomedical Engineering.

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